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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/590,026	08/18/2006	Nobuhiro Oikawa	OIKAWA1	5830

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EXAMINER	
RICCI, CRAIG D	

ART UNIT	PAPER NUMBER
1614	

MAIL DATE	DELIVERY MODE
10/15/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/590,026	OIKAWA ET AL.	
	Examiner	Art Unit	
	CRAIG RICCI	4161	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 September 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3 and 6-11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3 and 6-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/10/2007 and 08/01/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

1. Claims 1-3 and 6-11 are currently pending and the subject of this Office Action. Claims 4-5 are cancelled. This is the first Office Action on the merits of the claims.

Information Disclosure Statement

2. All references have been considered.

Priority

3. The earliest effective filing date afforded the instantly claimed invention has been determined to be 02/23/2005 as to claims 1-3 and 6-11.

4. Acknowledgment is made of Applicant's claims for foreign priority pursuant to 35 U.S.C. 119(a) and 365(b) based on prior applications filed in Japan on 02/23/2004 and 08/27/2004. However, the certified copies have **NOT** been received.

Election/Restrictions

5. Applicant's election with traverse of Group I in the reply filed on 08/25/2008 is acknowledged. Lack of unity was based on *Cirillo et al* (WO 2003/032989) which teaches compounds of the instant invention having a naphthyl in place of phenyl. Applicant traverses on that ground that there is no teaching or suggestion in *Cirillo et al* regarding substituting a naphthyl for a phenyl group. However, the bioisosteric substitution of phenyl for naphthyl is well known in the art and said substitution would have been obvious to one of ordinary skill in the art. Indeed, *Miller et al* (WO 1999/32436) teach structurally related "compounds which are inhibitors of the enzyme

raf kinase" (Page 2, Lines 6-7) and furthermore demonstrate either **naphthyl or phenyl** are alternatively usable in said compounds.

6. Applicant further elected compound Example 152. The elected species reads upon claims 1-3 and 6-11. Applicant timely traversed the restriction (election) requirement in the reply filed on 08/25/2008.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. **Claims 1-3 and 6-11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for some of the compound encompassed by the claims, does not reasonably provide enablement for all of the compounds encompassed by the claims**. Specifically, the specification does not enable any person skilled in the art to make and use the invention wherein W and Y^1 are as recited by instant claim 1. Applicant is enabled for compound wherein W is NRaRb, N=C(-Rc)NRaRb, N(-Ra)C(=O)Rc and N[C(=O)Rc][C(=O)Rc'] and wherein Y^1 is hydrogen. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

9. Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art

and the amount of experimentation necessary. All of the Wands factors have been considered, with the most relevant factors discussed below.

10. Nature of the invention: The invention is drawn to compounds which are alleged to be Raf inhibitors useful in the treatment of cancer, psoriasis, atherosclerosis, chronic rheumatoid arthritis and diabetes. It is well know and one of ordinary skill in the art would recognize that the development of specific kinase inhibitors is a complicated and complex undertaking.

11. Breadth of the claims: The claims, which recite a generic compound of formula (1) containing a number of variable groups, many of which contain additional variables, encompass thousands of compounds. In particular, instant claim 1 recites that Q is optionally substituted with at least one substituent W, wherein W can encompass thousands of potential substituents. Accordingly, the claims are broad. Furthermore, the broadness of the claims exacerbates the complexity of the invention in that the claims require that each of the thousands of distinct compound species to have the alleged activity; namely, that each and every of the compound species encompassed by the claims are Raf inhibitors.

12. Guidance of the specification/The existence of working examples: The specification provides evidence that 11 of the potentially thousands of compounds encompassed by the instant claims possess Raf inhibitory activity. In each of the 11 examples of compounds that possess Ran inhibitory activity, W is limited to NRaRb, N=C(-Rc)NRaRb, N(-Ra)C(=O)Rc and N[C(=O)Rc][C(=O)Rc']. Moreover, Y^1 was limited in each of the examples to hydrogen.

13. State of the art/Predictability of the art: Urea compounds useful as Raf inhibitors are well known in the art. However, it is also well known in the art that minor structural changes to these compounds will have a significant impact on the Raf inhibitory activity of each compound. As evidenced by *Khire et al* (Biorg Med Chem Lett 14:783-786, 2004) a shift from hydrogen to methyl in a terminal substituent in a urea Raf kinase inhibitor altered the Raf kinase IC50 (nM)[9] from 120 to 5800 (Page 784, Table I, compare Compound 2 with Compound 8). Accordingly, it would be impossible for one of ordinary skill in the art at the time the invention was made to reasonably predict which of the thousands of compounds encompassed by the variable W group possess anti Raf activity. The person of ordinary skill in the art would be required to make and test each of the compounds to determine which, if any, possess such activity.

14. Amount of experimentation necessary: In light of the complexity of the invention, coupled with the broadness of the claims which exacerbate the complexity, and further in light of the lack of guidance and unpredictability of the art, it would require undue experimentation in order to practice the claimed invention.

15. **Claims 1-3 and 6-11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making salts of the claimed compounds, does not reasonably provide enablement for making prodrugs of the claimed compounds**.

16. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art of medicinal chemistry to use the invention. Enablement is considered in view of the Wands factors (MPEP 2164.01(A)).

These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered, with the most relevant factors discussed below.

17. Nature of the invention: Claims 1-3 and 6-11 are drawn to compounds of formula (1) and a pharmaceutical composition comprising a compound of formula (1) as well as salts or prodrugs thereof. For a compound to be a prodrug, it must meet three tests: first, it must itself be biologically inactive; second, it must be metabolized to a second substance in a human at a rate and to an extent to produce that second substance at a physiologically meaningful concentration; and third, that second substance must be clinically effective. Finding a prodrug is an empirical exercise and determining whether a particular compound meets these three criteria in a clinical trial setting requires a large quantity of experimentation. For example, predicting if a certain ester of a claimed alcohol is in fact a prodrug that produces the active compound metabolically, in man, at a therapeutic concentration and at a useful rate is filled with experimental uncertainty. Although attempts have been made to predict drug metabolism *de novo*, this is still an experimental science.

18. Breadth of the claims: The claim encompasses not only the compound of formula (1), but also the presently unknown list of potential prodrugs of the compound of formula (1). Accordingly, the claim encompasses hundreds of thousands of compositions.

19. Guidance of the specification/The existence of working examples: The direction concerning the prodrugs is not found in the specification and there are no working examples of a prodrug of a compound of formula I.

20. State of the art/Predictability of the art: *Wolff, Manfred E* ((Burger's Medicinal Chemistry 5ed, Part I) John Wiley & Sons, 1995, pages 975-977) in the last paragraph on page 975 describes the artisans making Applicants' prodrugs as a collaborative team of synthetic pharmaceutical chemists and metabolism experts. All would have a Ph. D. degree and several years of industrial experience.

21. *Wolff* also summarizes the state of the prodrug art. The table on the left side of page 976 outlines the research program to be undertaken to find a prodrug. The second paragraph in section 10 and the paragraph spanning pages 976-977 indicate the low expectation of success. In that paragraph the difficulties of extrapolating between species are further developed. Since the prodrug concept is a pharmacokinetic issue, the lack of any standard pharmacokinetic protocol discussed in the last sentence of this paragraph is particularly relevant. Furthermore, *Banker* ((Modern Pharmaceutics) Banker, G.S. et al, "Modern Pharmaceutics, 3ed.", Marcel Dekker, New York, 1996, pages 451 and 596) in the first sentence, third paragraph on page 596, states that "extensive development must be undertaken" to find a prodrug.

22. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved" and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). h)

23. Amount of experimentation necessary: MPEP 2164.01(a) states, "[a] conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here. Thus, undue experimentation will be required to determine if any particular compound of unknown structure is, in fact, a prodrug.

24. **Claim 11 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for therapeutic agents does not reasonably provide enablement for making preventative agents**.

25. While Applicant has enabled a therapeutic agent for a disease such as cancer, psoriasis, atherosclerosis, etc as recited by instant claim 11 in the sense that Applicant enables an agent for reducing some of the consequences of those diseases in patients suffering from said conditions, curing and preventing the disease are not considered enabled. Accordingly, claim 11 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of diseases (conditions or disorders) as discussed, does not reasonably provide enablement for the prevention of such diseases. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

26. Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered, with the most relevant factors discussed below.

27. Nature of the invention: The nature of the invention is determined in part by the state of the prior art. Even a cursory perusal of the teachings of the medicinal arts reveals that they have not advanced to the point where complex conditions such as, inter alia, (cancer, psoriasis, atherosclerosis, etc) (claim 11) can in any way be said to be preventable. The art, in general, teaches, instead, that what may in some cases be prevented with regard to such diseases or disorders are their associated symptoms.

28. Breadth of the claims: The claims are broad in that they claim a preventative agent for said diseases the breadth of which exacerbates the complexity of the invention.

29. Guidance of the specification/The existence of working examples: The amount of direction provided by the Applicant is considered to be determined by the specification and the working examples. Applicant's data do not demonstrate that the instant invention is capable of preventing any disease or disorder.

30. State of the art/Predictability of the art: The level of predictability in the art is considered to be relatively low. The basis of all modern medicine and biology is, of course, chemistry. Yet even under the best of circumstances, and several hundred years after Lavoisier laid the foundations of its modern practice, chemistry remains and

experimental science. Neither the medicinal/biological arts nor the chemical arts upon which they are based have advanced to the point where certainty has replaced the need for clinical and/or laboratory experimentation.

31. Amount of experimentation necessary: Regardless of the amount of experimentation involved, Applicant's claim with respect to the prevention of numerous and various diseases and disorders enumerated in the specification is not believable in light of the present understanding in contemporary medicinal arts. It is settled case law that allegations of utility that are not believable in light of contemporary knowledge in the art must be substantiated by acceptable evidence or stricken from the specification. *In re Ferns*, 163 USPQ 609 (CCPA 1969); *Ex Parte Moore*, 129 USPQ 8 (BPAI 1960); *In re Hozumi*, 226 USPQ 353 (Comr. Dec 1985); MPEP 706.03(n) and 706.03(z).

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CRAIG RICCI whose telephone number is (571) 270-5864. The examiner can normally be reached on Monday through Thursday, and every other Friday, 7:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on (571) 272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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